CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074035

Trade Name : KETOPROFEN CAPSULES

Generic Name: Ketoprofen Capsules

Sponsor : Mylan Pharmaceuticals, Inc.

Approval Date: December 31, 1996

ANDA 74-035

DEC 31 '96

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated January 10, 1991, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketoprofen Capsules, 50 mg and 75 mg.

Reference is also made to your amendments dated July 5, 1995, and March 18, May 21, June 10, November 13, and November 25, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ketoprofen Capsules, 50 mg and 75 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Orudis® Capsules 50 mg and 75 mg, respectively, of Wyeth-Ayerst Laboratories, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 12/31/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-035
ANDA #74-035/Division File
Field Copy
HFD-600/Reading file
HFD-82
HFD-8/P/Savino
HFD-610/J.Phillips

Endorsements:
HFD-623/M.Maust/10/22/96 M. Maust 10-29-96
HFD-623/V.Sayeed, Ph.D./10/24/96 for Dr. Sayeed 10/30/96
HFD-617/R.West for J.Wilson, CSO/10/28/96
HFD-613/C.Park/10/28/96 10/29/96
HFD-613/J.Grace/A.Vezza for/10/29/96 A Vezza for J Grace 10-29-96
X:\NEW\FIRMSAM\MYLAN\LTRS&REV\74035R3.AD
F/T by: bc/10-29-96

APPROVAL

12/31/96

P Schwing for 11/1/96

1. CHEMISTRY REVIEW NO. 94 MM 11-14-96 2. ANDA # **74-035**

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc, Attention: Patrick Noonan
781 Chesnut Ridge Road, P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION Orudis® by Wyeth-Ayerst

5. SUPPLEMENTS N/A
6 PROPRIETARY NAME N/A
7. NONPROPRIETARY NAME **Ketoprofen Capsules**
8. SUPPLEMENTS PROVIDE FOR: N/A

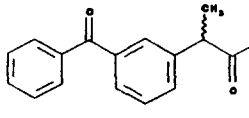
10. PHARMACOLOGICAL CATEGORY NSAID 11. Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM Oral, Capsules

14. POTENCY **50 mg**: No. 2 light celery opaque 0692 cap/body, hard shell gelatin capsule filled with a white to off-white powder imprinted "Mylan 4070" in black
75 mg: No. 2 light aqua opaque 0621 cap/light aqua opaque 0621 body, hard shell gelatin capsule filled with a white to off-white powder imprinted "Mylan 5750" in black

15. CHEMICAL NAME AND STRUCTURE Ketoprofen
$C_{16}H_{14}O_3$; M.W. = 254.28 CAS [22071-15-4]
m-Benzoylhydratropic acid.



16. RECORDS AND REPORTS N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS **APPROVE**

19. REVIEWER: Melissa Maust DATE COMPLETED: October 22, 1996

cc: ANDA 74-035
Division File

Endorsements:
HFD-623/M.Maust/M. Maust 10-22-96
HFD-623/V. Sayeed, Ph.D./ Vilayat Sayeed 10/24/96
X:\NEW\FIRMSAM\MYLAN\LTRS&REV\74035R3.AD
F/T by

MYLAN P

KETOPROF

ANDA 74-

3 0378-4070-10 9

50 mg

Each capsule contains:
Ketoprofen .... 50 mg

DEC 31 1996

NDC 0378-4070-10

MYLAN®

KETOPROFEN CAPSULES 50 mg

1000 CAPSULES

dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM407

---

3 0378-4070-01 7

50 mg

Each capsule contains:
Ketoprofen ...... 50 mg

DEC 31 1996

NDC 0378-4070-01

MYLAN®

KETOPROFEN CAPSULES 50 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM4070A1

---

3 0378-4070-01 7

50 mg

Each capsule contains:
Ketoprofen ...... 50 mg

DEC 31 1996

NDC 0378-4070-01

MYLAN®

KETOPROFEN CAPSULES 50 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM4070A1

---

3 0378-4070-01 7

50 mg

Each capsule contains:
Ketoprofen ...... 50 mg

DEC 31 1996

NDC 0378-4070-01

MYLAN®

KETOPROFEN CAPSULES 50 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM4070A1

---

3 0378-4070-01 7

50 mg

Each capsule contains:
Ketoprofen ...... 50 mg

DEC 31 1996

NDC 0378-4070-01

MYLAN®

KETOPROFEN CAPSULES 50 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM4070A1

Each capsule contains:
Ketoprofen .... 75 mg

NDC 0378-5750-10

MYLAN®

KETOPROFEN CAPSULES 75 mg

1000 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM5750C1

3 N 0378-5750-10 9

75 mg

APPROVED DEC 31 1996

Each capsule contains:
Ketoprofen .... 75 mg

NDC 0378-5750-01

MYLAN®

KETOPROFEN CAPSULES 75 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM5750A1

3 N 0378-5750-01 7

75 mg

AP DEC 31 1996

Each capsule contains:
Ketoprofen .... 75 mg

NDC 0378-5750-01

MYLAN®

KETOPROFEN CAPSULES 75 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM5750A1

3 N 0378-5750-01 7

75 mg

APP DEC 31 1996

Each capsule contains:
Ketoprofen .... 75 mg

NDC 0378-5750-01

MYLAN®

KETOPROFEN CAPSULES 75 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM5750A1

3 N 0378-5750-01 7

75 mg

AP DEC 31 1996

Each capsule contains:
Ketoprofen .... 75 mg

NDC 0378-5750-01

MYLAN®

KETOPROFEN CAPSULES 75 mg

100 CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: See insert.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM5750A1

3 N 0378-5750-01 7

75 mg

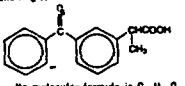
AP DEC 31 1996

KET:R3

KETOPROFEN CAPSULES

50 mg and 75 mg

DESCRIPTION: Ketoprofen is a nonsteroidal anti-inflammatory drug. The chemical name for ketoprofen is 2-(3-benzoylphenyl)propionic acid with the following structural formula:



Its molecular formula is $C_{16}H_{14}O_3$ with a molecular weight of 254.29. It has a pKa of 5.94 in methanol:water (3:1) and a n-octanol:water partition coefficient of 0.97 (buffer pH 7.4). Ketoprofen is a white or off-white, odorless, nonhygroscopic, fine to granular powder, melting at about 95°C. It is freely soluble in ethanol, chloroform, acetone, ether and soluble in benzene and strong alkali, but practically insoluble in water at 20°C.

Each capsule for oral administration contains 50 mg or 75 mg of ketoprofen and the following inactive ingredients: colloidal silicon dioxide, gelatin, lactose monohydrate, magnesium stearate, pharmaceutical glaze, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, starch, and titanium dioxide. The following coloring agents are employed:

50 mg – FD&C Blue #1, D&C Yellow #10, FD&C Yellow #6, synthetic black iron oxide, FD&C Blue #2, and FD&C Red #40.

75 mg – FD&C Blue #1, FD&C Green #3, synthetic black iron oxide, FD&C Blue #2, FD&C Red #40, and D&C Yellow #10

CLINICAL PHARMACOLOGY: Ketoprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties.

The anti-inflammatory, analgesic, and antipyretic properties of ketoprofen have been demonstrated in classical animal and *in vitro* test systems. In anti-inflammatory models ketoprofen has been shown to have inhibitory effects on prostaglandin and leukotriene synthesis, to have antibradykinin activity, as well as to have lysosomal membrane-stabilizing action. However, its mode of action, like that of other nonsteroidal anti-inflammatory drugs, is not fully understood.

Pharmacodynamics: Ketoprofen is a racemate with only the S enantiomer possessing pharmacological activity. The enantiomers have similar concentration time curves and do not appear to interact with one another.

Pharmacokinetics: *General:* The systemic availability (F_a) when the oral formulation is compared with IV administration is approximately 90% in humans. For 75 mg to 200 mg single doses, the area under the curve has been shown to be dose proportional.

Ketoprofen is >99% bound to plasma proteins, mainly to albumin.

Absorption: Ketoprofen is rapidly and well-absorbed, with peak plasma levels occurring within 0.5 to 2 hours.

When ketoprofen is administered with food, its total bioavailability (AUC) is not altered; however, the rate of absorption is slowed.

Food intake reduces C_{max} by approximately one-half and increases the mean time to peak concentration (t_{max}) from 1.2 hours for fasting subjects (range, 0.5 to 3 hours) to 2 hours for fed subjects (range, 0.75 to 3 hours). The

possessing pharmacological activity.
The enantiomers have similar concentration time curves and do not appear to interact with one another.

Pharmacokinetics: *General:* The systemic availability (F_a) when the oral formulation is compared with IV administration is approximately 90% in humans. For 75 mg to 200 mg single doses, the area under the curve has been shown to be dose proportional.

Ketoprofen is >99% bound to plasma proteins, mainly to albumin.

Absorption: Ketoprofen is rapidly and well-absorbed, with peak plasma levels occurring within 0.5 to 2 hours.

When ketoprofen is administered with food, its total bioavailability (AUC) is not altered; however, the rate of absorption is slowed.

Food intake reduces C_{max} by approximately one-half and increases the mean time to peak concentration (t_{max}) from 1.2 hours for fasting subjects (range, 0.5 to 3 hours) to 2 hours for fed subjects (range, 0.75 to 3 hours). The fluctuation of plasma peaks may also be influenced by circadian changes in the absorption process.

Concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with absorption of ketoprofen.

Metabolism: The metabolic fate of ketoprofen is glucuronide conjugation to form an unstable acyl-glucuronide. The glucuronic acid moiety can be converted back to the parent compound. Thus, the metabolite serves as a potential reservoir for parent drug, and this may be important in persons with renal insufficiency, whereby the conjugate may accumulate in the serum and undergo deconjugation back to the parent drug (see Special Populations: Renally Impaired). The conjugates are reported to appear only in trace amounts in plasma in healthy adults, but are higher in elderly subjects—presumably because of reduced renal clearance. It has been demonstrated that in elderly subjects following multiple doses (50 mg every 6 hours) the ratio of conjugated to parent ketoprofen AUC was 30% and 3%, respectively, for the S and R enantiomers.

There are no known active metabolites of ketoprofen. Ketoprofen has been shown not to induce drug-metabolizing enzymes.

Elimination: The plasma clearance of ketoprofen is approximately 0.08 L/kg/h with a V_d of 0.1 L/kg after IV administration. The elimination half-life of ketoprofen has been reported to be 2.05 ± 0.58 hours (Mean ± S.D.) following IV administration and from 2 to 4 hours following ketoprofen capsules. In cases of slow drug absorption, the elimination rate is dependent on the absorption rate and thus $t_{1/2}$ relative to an IV dose appears prolonged.

In a 24-hour period, approximately 80% of an administered dose of ketoprofen is excreted in the urine, primarily as the glucuronide metabolite.

Enterohepatic recirculation of the drug has been postulated, although biliary levels have never been measured to confirm this.

Special Populations: Elderly: Clearance and Unbound Fraction: The plasma and renal clearance of ketoprofen is reduced in the elderly (mean age, 73 years) compared to a younger normal population (mean age, 27 years). Hence, ketoprofen peak concentration and AUC increase with increasing age. In addition, there is a corresponding increase in unbound fraction with increasing age. Data from one trial suggest that the increase is greater in women than in men. It has not been determined whether age-related changes in absorption among the elderly contribute to the changes in bioavailability of ketoprofen.

In a study conducted with young and elderly men and women, results for subjects older than 75 years of age showed that free drug AUC increased by 40% and C_{max} increased by 60% as compared with estimates of the same parameters in young subjects (those younger than 35 years of age; see Individualization of Dosage).

Also in the elderly, the ratio of intrinsic clearance/availability decreased by 35% and plasma half-life was prolonged by 26%. This reduction is thought to be due to a decrease in hepatic extraction associated with aging.

Compared to the younger subject group, the elimination half-life in the elderly was prolonged by 54% and total drug C_{max} and AUC were 40% and 70% higher, respectively. Plasma concentrations in the elderly after single doses and at steady state were essentially the same. Thus, no drug accumulation occurs.

In comparison to younger subjects taking the immediate release ketoprofen capsules, there was a decrease of 16% and 25% in total drug C_{max} and AUC, respectively, among the elderly.

Renally Impaired: Studies of the effects of renal-function impairment have been small. They indicate a decrease in clearance in patients with impaired renal function. In 23 patients with renal impairment, free ketoprofen peak concentration was not significantly elevated, but free ketoprofen clearance was reduced from 15 L/kg/h for normal subjects to 7 L/kg/h in patients with mildly impaired renal function, and to 4 L/kg/h in patients with moderately to severely impaired renal function. The elimination $t_{1/2}$ was prolonged from 1.6 hours in normal subjects to approximately 3 hours in patients with mild renal impairment, and to approximately 5 to 9 hours in patients with moderately to severely impaired renal function.

It is recommended that only the immediate release ketoprofen capsules be used to treat patients with signifi-

but free ketoprofen clearance was reduced from 15 L/kg/h for normal subjects to 7 L/kg/h in patients with mildly impaired renal function, and to 4 L/kg/h in patients with moderately to severely impaired renal function. The elimination $t_{1/2}$ was prolonged from 1.6 hours in normal subjects to approximately 3 hours in patients with mild renal impairment, and to approximately 5 to 9 hours in patients with moderately to severely impaired renal function.

It is recommended that only the immediate release ketoprofen capsules be used to treat patient: with significant renal impairment (see Individualization of Dosage).

Hepatically Impaired: For patients with alcoholic cirrhosis, no significant changes in the kinetic disposition of immediate release ketoprofen capsules were observed relative to age-matched normal subjects: the plasma clearance of drug was 0.07 L/kg/h in 26 hepatically impaired patients. The elimination half-life was comparable to that observed for normal subjects. However, the unbound (biologically active) fraction was approximately doubled, probably due to hypoalbuminemia and high variability which was observed in the pharmacokinetics for cirrhotic patients. Therefore, these patients should be carefully monitored and daily doses of ketoprofen kept at the minimum providing the desired therapeutic effect. It is recommended that only immediate release ketoprofen be used in treat patients who have hepatic impairment and serum albumin levels below 3.5 g/dL (see Individualization of Dosage).

Clinical Trials: Rheumatoid Arthritis And Osteoarthritis: The efficacy of ketoprofen has been demonstrated in patients with rheumatoid arthritis and osteoarthritis. In other trials, ketoprofen demonstrated effectiveness comparable to aspirin, ibuprofen, naproxen, piroxicam, diclofenac and indomethacin. In some of these studies there were more dropouts due to gastrointestinal side effects among patients on ketoprofen than among patients on other NSAIDs.

In studies with patients with rheumatoid arthritis, ketoprofen was administered in combination with gold salts, antimalarials, low-dose methotrexate, d-penicillamine, and/or corticosteroids with results comparable to those seen with control nonsteroidal drugs.

Individualization Of Dosage: In patients with significant renal impairment, immediate release ketoprofen should be used. The initial dosage should be reduced to 25 mg to 50 mg TID in patients with mildly impaired renal function and to 25 mg to 50 mg twice daily (BID) in patients with a more severe renal impairment (GFR less than 25 mL/min/1.73 m^2 or end-stage renal insufficiency). In elderly patients, renal function may be reduced with comparatively normal serum creatinine and/or BUN levels. Therefore, immediate release ketoprofen capsules are the recommended formulation of ketoprofen and the initial dosage for patients over 75 years of age should be reduced to 75 mg to 150 mg/day.

It is recommended that for patients with impaired liver function and serum albumin concentration less than 3.5 g/dL, immediate release ketoprofen capsules should be used and the initial dosage reduced to 75 to 150 mg/day. All patients with cirrhotic impairment, particularly those with both hypoalbuminemia and reduced renal function, may have increased levels of free biologically active) ketoprofen and should be closely monitored. The dosage may be increased to the range recommended for the general population, if necessary, only after good individual tolerance has been ascertained.

DEC 31 1996

Because hypoalbuminemia and reduced renal function both increase the fraction of free drug (biologically active form), patients who have both conditions may be at greater risk of adverse effects. Therefore, it is recommended that such patients also be started on lower doses of ketoprofen and closely monitored.

As with other nonsteroidal anti-inflammatory drugs, the predominant adverse effects of ketoprofen are gastrointestinal. To attempt to minimize these effects, physicians may wish to prescribe that ketoprofen be taken with antacids, food, or milk. Although food delays the absorption (see CLINICAL PHARMACOLOGY), in most of the clinical trials ketoprofen was taken with food or milk.

Physicians may want to make specific recommendations to patients about when they should take ketoprofen in relation to food and/or what patients should do if they experience minor GI symptoms.

INDICATIONS AND USAGE: Ketoprofen capsules are indicated for the management of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Ketoprofen capsules are indicated for the relief of mild-to-moderate pain. Ketoprofen capsules are also indicated for treatment of primary dysmenorrhea.

CONTRAINDICATIONS: Ketoprofen is contraindicated in patients who have shown hypersensitivity to it. Ketoprofen should not be given to patients in whom aspirin or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions, because severe, rarely fatal, anaphylactic reactions to ketoprofen have been reported in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding, and Perforation with NSAID Therapy: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper-gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy.

therefore, it is recommended that such patients also be started on lower doses of ketoprofen and closely monitored.

As with other nonsteroidal anti-inflammatory drugs, the predominant adverse effects of ketoprofen are gastrointestinal. To attempt to minimize these effects, physicians may wish to prescribe that ketoprofen be taken with antacids, food, or milk. Although food delays the absorption (see CLINICAL PHARMACOLOGY), in most of the clinical trials ketoprofen was taken with food or milk.

Physicians may want to make specific recommendations to patients about when they should take ketoprofen in relation to food and/or what patients should do if they experience minor GI symptoms.

INDICATIONS AND USAGE: Ketoprofen capsules are indicated for the management of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Ketoprofen capsules are indicated for the relief of mild-to-moderate pain. Ketoprofen capsules are also indicated for treatment of primary dysmenorrhea.

CONTRAINDICATIONS: Ketoprofen is contraindicated in patients who have shown hypersensitivity to it. Ketoprofen should not be given to patients in whom aspirin or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions, because severe, rarely fatal, anaphylactic reactions to ketoprofen have been reported in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding, and Perforation with NSAID Therapy: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper-gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper-GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no other risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Ketoprofen and other nonsteroidal anti-inflammatory drugs cause nephritis in mice and rats associated with chronic administration. Rare cases of interstitial nephritis and nephrotic syndrome have been reported with ketoprofen since it has been marketed.

A second form of renal toxicity has been seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal blood flow. In these patients, administration of a nonsteroidal anti-inflammatory drug results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in renal blood flow which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Since ketoprofen is primarily eliminated by the kidneys and its pharmacokinetics are altered by renal failure (see CLINICAL PHARMACOLOGY), patients with significantly impaired renal function should be closely monitored, and a reduction of dosage should be anticipated to avoid accumulation of ketoprofen and/or its metabolites (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may disappear with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of ALT or AST (SGOT) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ketoprofen. Serious hepatic reactions, including jaundice, have been reported from post-marketing experience with ketoprofen as well as with other nonsteroidal anti-inflammatory drugs.

In patients with chronic liver dis-

[illegible] considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Ketoprofen and other nonsteroidal anti-inflammatory drugs cause nephritis in mice and rats associated with chronic administration. Rare cases of interstitial nephritis and nephrotic syndrome have been reported with ketoprofen since it has been marketed.

A second form of renal toxicity has been seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal blood flow. In these patients, administration of a nonsteroidal anti-inflammatory drug results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in renal blood flow which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pre-treatment state.

Since ketoprofen is primarily eliminated by the kidneys and its pharmacokinetics are altered by renal failure (see CLINICAL PHARMACOLOGY), patients with significantly impaired renal function should be closely monitored, and a reduction of dosage should be anticipated to avoid accumulation of ketoprofen and/or its metabolites (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may disappear with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of ALT or AST (SGOT) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ketoprofen. Serious hepatic reactions, including jaundice, have been reported from post-marketing experience with ketoprofen as well as with other nonsteroidal anti-inflammatory drugs.

In patients with chronic liver disease with reduced serum albumin levels, ketoprofen's pharmacokinetics are altered (see CLINICAL PHARMACOLOGY). Such patients should be closely monitored, and a reduction of dosage should be anticipated to avoid high blood levels of ketoprofen and/or its metabolites (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

If steroid dosage is reduced or eliminated during therapy, it should be reduced slowly and the patients observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by nonsteroidal anti-inflammatory drugs, which may produce fluid retention or significant gastrointestinal blood loss in some patients. Patients on long-term treatment with NSAIDs, including ketoprofen, should have their hemoglobin or hematocrit checked if they develop signs or symptoms of anemia.

Peripheral edema has been observed in approximately 2% of patients taking ketoprofen. Therefore, as with other nonsteroidal anti-inflammatory drugs, ketoprofen should be used with caution in patients with fluid retention, hypertension, or heart failure.

Information for Patients: Ketoprofen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious. Physicians may wish to discuss with their patients the potential risks (see WARNINGS: PRECAUTIONS, General and ADVERSE REACTIONS sections) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs might represent an acceptable alternative to both the patient and physician.

Because aspirin causes an increase in the level of unbound ketoprofen, patients should be advised not to take aspirin while taking ketoprofen (see Drug Interactions). It is possible that minor adverse symptoms of gastric intolerance may be prevented by administering ketoprofen with antacids, food, or milk. Because food and milk do affect the rate but not the extent of absorption (see CLINICAL PHARMACOLOGY), physicians may want to make specific recommendations to patients about when they should take ketoprofen in relation to food and/or what patients should do if they experience minor GI symptoms associated with ketoprofen therapy.

Laboratory Tests: Because serious GI-tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS, Risk of GI Ulceration, Bleeding, and Perforation with NSAID Therapy).

Drug Interactions: The following drug interactions were studied with ketoprofen doses of 200 mg per day. The possibility of increased interaction should be kept in mind when ketoprofen doses greater than 50 mg as a single dose or 200 mg of ketoprofen per day are used concomitantly with highly bound drugs.

1. Antacids: Concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with the rate or extent of the absorption of ketoprofen.

2. Aspirin: Ketoprofen does not alter aspirin absorption; however, in a study of 12 normal subjects, concurrent administration of aspirin decreased ketoprofen protein binding and increased ketoprofen plasma clearance from 0.07 L/kg/hr without aspirin to 0.11 L/kg/hr with aspirin. The clinical significance of these changes has not been adequately studied. Therefore, concurrent use of aspirin and ketoprofen is not recommended.

3. Diuretic: Hydrochlorothiazide, given concomitantly with ketoprofen, produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition (see PRECAUTIONS: General).

4. Digoxin: In a study in 12 patients with congestive heart failure where ketoprofen and digoxin were concomitantly administered, ketoprofen did not alter the serum levels of digoxin.

5. Warfarin: In a short-term controlled study in 14 normal volunteers, ketoprofen did not significantly interfere with the effect of warfarin on prothrombin time. Bleeding from a number of sites may be a complication of warfarin treatment and GI bleeding a complication of ketoprofen treatment. Because prostaglandins play an important role in hemostasis and ketoprofen has an effect on platelet function as well (see Drug/Laboratory Test Interactions: *Effect on Blood Coagulation*), concurrent therapy with ketoprofen and warfarin requires close monitoring of patients on both drugs.

6. Probenecid: Probenecid increases both free and bound ketoprofen by reducing the plasma clearance of ketoprofen to about one-third, as well as decreasing its protein binding. Therefore, the combination of ketoprofen and probenecid is not recommended.

7. Methotrexate: Ketoprofen, like other NSAIDs, may cause changes in the elimination of methotrexate leading to elevated serum levels of the drug and increased toxicity.

8. Lithium: Nonsteroidal anti-inflammatory agents have been reported to increase steady-state plasma lithium levels. It is recommended that plasma lithium levels be monitored when ketoprofen is co-administered with lithium.

Drug/Laboratory Test Interactions: *Effect on Blood Coagulation:* Ketoprofen decreases platelet adhesion and aggregation. Therefore, it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. There is no significant change in platelet count, prothrombin time, partial thromboplastin time, or thrombin time.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in mice (up to 32 mg/kg/day; 96 mg/m^2/day) did not indicate a carcinogenic potential for ketoprofen. The maximum recommended human therapeutic dose is 800 mg/day for a 60 kg patient with a body surface area of 1.6 m^2, which is 5 mg/kg/day or 185 mg/m^2/day. Thus the mice were treated at 0.5 times the maximum human daily dose based on surface area.

A 2-year carcinogenicity study in rats, using doses up to 6 mg/kg/day (36 mg/m^2/day), showed no evidence of tumorigenic potential. All groups were treated for 104 weeks except the females receiving 6 mg/kg/day (36 mg/m^2/day) where the drug treatment was terminated in week 81 because of low survival; the remaining rats were sacrificed after

decreases platelet aggregation and aggregation. Therefore, it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. There is no significant change in platelet count, prothrombin time, partial thromboplastin time, or thrombin time.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in mice (up to 32 mg/kg/day; 96 mg/m^2/day) did not indicate a carcinogenic potential for ketoprofen. The maximum recommended human therapeutic dose is 300 mg/day for a 60 kg patient with a body surface area of 1.6 m^2, which is 5 mg/kg/day or 185 mg/m^2/day. Thus the mice were treated at 6.5 times the maximum human daily dose based on surface area.

A 2-year carcinogenicity study in rats, using doses up to 6 mg/kg/day (36 mg/m^2/day), showed no evidence of tumorigenic potential. All groups were treated for 104 weeks except the females receiving 6 mg/kg/day (36 mg/m^2/day) where the drug treatment was terminated in week 81 because of low survival; the remaining rats were sacrificed after week 87. Their survival in the groups treated for 104 weeks was within 6% of the control group. An earlier 2-year study with doses up to 12.5 mg/kg/day (75 mg/m^2/day) also showed no evidence of tumorigenicity, but the survival rate was low and the study was therefore judged inconclusive. Ketoprofen did not show mutagenic potential in the Ames Test. Ketoprofen administered to male rats (up to 9 mg/kg/day; or 54 mg/m^2/day) had no significant effect on reproductive performance or fertility. In female rats administered 6 or 9 mg/kg/day (36 or 54 mg/m^2/day), a decrease in the number of implantation sites has been noted. The dosages of 36 mg/m^2/day in rats represent 0.2 times the maximum recommended human dose of 185 mg/m^2/day (see above).

Abnormal spermatogenesis or inhibition of spermatogenesis developed in rats and dogs at high doses, and a decrease in the weight of the testes occurred in dogs and baboons at high doses.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** In teratology studies ketoprofen administered to mice at doses up to 12 mg/kg/day (36 mg/m^2/day) and rats at doses up to 9 mg/kg/day (54 mg/m^2/day), the approximate equivalent of 0.2 times the maximum recommended therapeutic dose of 185 mg/m^2/day, showed no teratogenic or embryotoxic effects. In separate studies in rabbits, maternally toxic doses were associated with embryotoxicity but not teratogenicity.

There are no adequate and well-controlled studies in pregnant women. Because animal teratology studies are not always predictive of the human response, ketoprofen should be used during pregnancy only if the potential benefit justifies the risk.

Labor and Delivery: The effects of ketoprofen on labor and delivery in pregnant women are unknown. Studies in rats have shown ketoprofen at doses of 6 mg/kg (36 mg/m^2/day, approximately equal to 0.2 times the maximum recommended human dose) prolongs pregnancy when given before the onset of labor. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of ketoprofen during late pregnancy should be avoided.

Nursing Mothers: Data on secretion in human milk after ingestion of ketoprofen do not exist. In rats, ketoprofen at doses of 9 mg/kg (54 mg/m^2/day, approximately 0.3 times the maximum human therapeutic dose) did not affect perinatal development. Upon administration to lactating dogs, the milk concentration of ketoprofen was found to be 4 to 5% of the plasma drug level. As with other drugs that are excreted in milk, ketoprofen is not recommended for use in nursing mothers.

Pediatric Use: Ketoprofen is not recommended for use in pediatric patients, because its safety and effectiveness have not been studied in pediatric patients.

ADVERSE REACTIONS: The incidence of common adverse reactions (above 1%) was obtained from a population of 835 ketoprofen-treated patients in double-blind trials lasting from 4 to 54 weeks and in 822 patients treated with ketoprofen extended-release capsules in trials lasting from 4 to 16 weeks.

Minor gastrointestinal side effects predominated; upper gastrointestinal symptoms were more common than lower gastrointestinal symptoms. In crossover trials in 321 patients with rheumatoid arthritis or osteoarthritis, there was no difference in either upper or lower gastrointestinal symptoms between patients treated with 200 mg of ketoprofen extended-release capsules once a day or 75 mg of ketoprofen immediate release TID (225 mg/day). Peptic ulcer or GI bleeding occurred in controlled clinical trials in less than 1% of 1,076 patients; however, in open label continuation studies in 1,292 patients the rate was greater than 2%.

The incidence of peptic ulceration in patients on NSAIDs is dependent on many risk factors, including age, sex, smoking, alcohol use, diet, stress, concomitant drugs such as aspirin and corticosteroids, as well as the dose and duration of treatment with NSAIDs (see WARNINGS).

Gastrointestinal reactions were followed in frequency by central nervous system side effects, such as headache, dizziness, or drowsiness. The incidence of some adverse reactions appears to be dose-related (see DOSAGE AND ADMINISTRATION). Rare adverse reactions (incidence less than 1%) were collected

because its safety and effectiveness have not been studied in pediatric patients.

ADVERSE REACTIONS: The incidence of common adverse reactions (above 1%) was obtained from a population of 835 ibuprofen-treated patients in double-blind trials lasting from 4 to 54 weeks and in 622 patients treated with ibuprofen extended-release capsules in trials lasting from 4 to 16 weeks.

Minor gastrointestinal side effects predominated; upper gastrointestinal symptoms were more common than lower gastrointestinal symptoms. In crossover trials in 321 patients with rheumatoid arthritis or osteoarthritis, there was no difference in either upper or lower gastrointestinal symptoms between patients treated with 200 mg of ibuprofen extended-release capsules once a day or 75 mg of ibuprofen immediate release TID (225 mg/day). Peptic ulcer or GI bleeding occurred in controlled clinical trials in less than 1% of 1,876 patients; however, in open label continuation studies in 1,292 patients the rate was greater than 2%.

The incidence of peptic ulceration in patients on NSAIDs is dependent on many risk factors, including age, sex, smoking, alcohol use, diet, stress, concomitant drugs such as aspirin and corticosteroids, as well as the dose and duration of treatment with NSAIDs (see WARNINGS).

Gastrointestinal reactions were followed in frequency by central nervous system side effects, such as headache, dizziness, or drowsiness. The incidence of some adverse reactions appears to be dose-related (see DOSAGE AND ADMINISTRATION). Rare adverse reactions (incidence less than 1%) were collected from foreign reports to manufacturers and regulatory agencies, publications, and U.S. clinical trials.

Reactions are listed below under body system, then by incidence or number of cases in decreasing incidence.

Incidence Greater Than 1% (Probable Causal Relationship):

Digestive: Dyspepsia (11%), nausea*, abdominal pain*, diarrhea*, constipation*, flatulence*, anorexia, vomiting, stomatitis.

Nervous System: Headache*, dizziness, CNS inhibition (i.e., pooled reports of somnolence, malaise, depression, etc.) or excitation (i.e., insomnia, nervousness, dreams, etc.)*.

Skin and Appendages: Rash.

Special Senses: Tinnitus, visual disturbance.

Urogenital: Impairment of renal function (edema, increased BUN)*, signs or symptoms of urinary-tract irritation.

*Adverse events occurring in 3 to 9% of patients.

Incidence Less Than 1% (Probable Causal Relationship):

Body as a Whole: Chills, facial edema, infection, pain, allergic reaction, anaphylaxis.

Cardiovascular: Hypertension, palpitation, tachycardia, congestive heart failure, peripheral vascular disease, vasodilation.

Digestive: Appetite increased, dry mouth, eructation, gastritis, rectal hemorrhage, melena, fecal occult blood, salivation, peptic ulcer, gastrointestinal perforation, hematemesis, intestinal ulceration.

Hemic: Hypocoagulability, agranulocytosis, anemia, hemolysis, purpura, thrombocytopenia.

Metabolic and Nutritional: Thirst, weight gain, weight loss, hepatic dysfunction, hyponatremia.

Musculoskeletal: Myalgia.

Nervous System: Amnesia, confusion, impotence, migraine, paresthesia, vertigo.

Respiratory: Dyspnea, hemoptysis, epistaxis, pharyngitis, rhinitis, bronchospasm, laryngeal edema.

Skin and Appendages: Alopecia, eczema, pruritus, purpuric rash, sweating, urticaria, bullous rash, exfoliative dermatitis, photosensitivity, skin discoloration, onycholysis.

Special Senses: Conjunctivitis, conjunctivitis sicca, eye pain, hearing impairment, retinal hemorrhage and pigmentation change, taste perversion.

Urogenital: Glomerulonephritis, hematuria, renal failure, interstitial nephritis, nephrotic syndrome.

Incidence Less Than 1% (Causal Relationship Unknown):

The following rare adverse reactions, whose causal relationship to ketoprofen is uncertain, are being listed to serve as alerting information to the physician.

Body as a Whole: Septicemia, shock.

Cardiovascular: Arrhythmias, myocardial infarction.

Digestive: Buccal necrosis, ulcerative colitis, microvesicular steatosis, jaundice, pancreatitis.

Endocrine: Diabetes mellitus (aggravated).

Nervous System: Dysphoria, hallucination, libido disturbance, nightmares, personality disorder, aseptic meningitis.

Urogenital: Acute tubulopathy, gynecomastia.

OVERDOSAGE: Signs and symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Respiratory depression, coma, or convulsions have occurred following large ketoprofen overdoses. Gastrointestinal bleeding, hypotension, hypertension, or acute renal failure may occur, but are rare.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients with symptoms seen within 4 hours or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in

Urogenital: Acute tubulopathy, gynecomastia.

OVERDOSAGE: Signs and symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Respiratory depression, coma, or convulsions have occurred following large ketoprofen overdoses. Gastrointestinal bleeding, hypotension, hypertension, or acute renal failure may occur, but are rare.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients with symptoms seen within 4 hours or following a large overdose (5 to 10 times the usual dose). This should be accomplished via means similar activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with a saline cathartic or sorbitol added to the first dose. Forced diuresis, alkalinization of the urine, hemodialysis or hemoperfusion would probably not be useful due to ketoprofen's high protein-binding.

Case reports include 26 overdoses: 6 were in children, 16 in adolescents, and 4 in adults. Five of these patients had minor symptoms (vomiting in 4, drowsiness in 1 child). A 12-year-old girl had tonic-clonic convulsions 1 to 2 hours after ingesting an unknown quantity of ketoprofen and 1 or 2 tablets of acetaminophen with hydrocodone. Her ketoprofen level was 1128 mg/L (56 times the upper therapeutic level of 20 mg/L) 3 to 4 hours post ingestion. Full recovery ensued 18 hours after ingestion following management with intubation, diazepam, and activated charcoal.

DOSAGE AND ADMINISTRATION: Rheumatoid Arthritis and Osteoarthritis: The recommended starting dose of ketoprofen in otherwise healthy patients is 75 mg three times or 50 mg four times a day. A smaller dose should be utilized initially in small individuals, in debilitated or elderly patients. The recommended maximum daily dose of ketoprofen is 300 mg/day (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

During titration, if minor side effects appear, they may disappear at a lower dose which may still have an adequate therapeutic effect. If well tolerated but not optimally effective, the dosage may be increased. Individual patients may show a better response to 300 mg daily as compared to 200 mg, although in well-controlled clinical trials patients on 300 mg did not show greater mean effectiveness. They did, however, show an increased frequency of upper- and lower-GI distress and headaches. It is of interest that women also had an increased frequency of these adverse effects compared to men. When treating patients with 300 mg/day, the physician should observe sufficient increased clinical benefit to offset potential increased risk. Dosages higher than 300 mg/day are not recommended because they have not been adequately studied. Relatively smaller people may need smaller doses. (See CLINICAL PHARMACOLOGY, Individualization of Dosage.)

Mild-to-Moderate Pain and Dysmenorrhea: The usual dose of ketoprofen recommended for mild-to-moderate pain and dysmenorrhea is 25 to 50 mg every 6 to 8 hours as necessary. A smaller dose should be utilized initially in small individuals, in debilitated or elderly patients, or in patients with renal or liver disease (see PRECAUTIONS, General). A larger dose may be tried if the patient's response to a previous dose was less than satisfactory, but doses above 75 mg have not been shown to give added analgesia. Daily doses above 300 mg are not recommended because they have not been adequately studied. Because of its typical nonsteroidal anti-inflammatory drug-side-effect profile, including as its principal adverse effect GI side effects (see WARNINGS and ADVERSE REACTIONS), higher doses of ketoprofen should be used with caution and patients receiving them observed carefully (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

HOW SUPPLIED: Ketoprofen capsules are available containing 50 mg or 75 mg of ketoprofen.

The 50 mg capsules are light celery opaque/light celery opaque marked in black ink with MYLAN 4070 on both the body and cap. They are available as follows:

NDC 0378-4070-01
bottles of 100 capsules
NDC 0378-4070-10
bottles of 1000 capsules

The 75 mg capsules are light aqua opaque/light aqua opaque marked in black ink with MYLAN 5750 on both the body and cap. They are available as follows:

NDC 0378-5750-01
bottles of 100 capsules
NDC 0378-5750-10
bottles of 1000 capsules

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

MYLAN®

Mild-to-Moderate Pain and Dysmenorrhea: The usual dose of ketoprofen recommended for mild-to-moderate pain and dysmenorrhea is 25 to 50 mg every 6 to 8 hours as necessary. A smaller dose should be utilized initially in small individuals, in debilitated or elderly patients, or in patients with renal or liver disease (see PRECAUTIONS, General). A larger dose may be tried if the patient's response to a previous dose was less than satisfactory, but doses above 75 mg have not been shown to give added analgesia. Daily doses above 300 mg are not recommended because they have not been adequately studied. Because of its typical nonsteroidal anti-inflammatory drug-side-effect profile, including as its principal adverse effect GI side effects (see WARNINGS and ADVERSE REACTIONS), higher doses of ketoprofen should be used with caution and patients receiving them observed carefully (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

HOW SUPPLIED: Ketoprofen capsules are available containing 50 mg or 75 mg of ketoprofen.

The 50 mg capsules are light celery opaque/light celery opaque marked in black ink with MYLAN 4070 on both the body and cap. They are available as follows:

NDC 0378-4070-01
bottles of 100 capsules
NDC 0378-4070-10
bottles of 1000 capsules

The 75 mg capsules are light aqua opaque/light aqua opaque marked in black ink with MYLAN 5750 on both the body and cap. They are available as follows:

NDC 0378-5750-01
bottles of 100 capsules
NDC 0378-5750-10
bottles of 1000 capsules

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED NOVEMBER 1996
KET-R3

[redacted]

JUN - 9 1992 **FILE COPY**

Ketoprofen Capsules
50 mg and 75 mg
ANDA # 74-035
Reviewer: Beatrice P. Chen
74035P.592

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
May 26, 1992

Review Of An In-Vivo Bioequivalence Study Protocol (Under Fasting Condition)

The firm is submitting a protocol for bioequivalence study under fasting condition on its test product, ketoprofen 75 mg capsule, comparing it with Wyeth-Ayerst's Orudis^R 75 mg capsule.

I. Background:

The firm has conducted and submitted two (fasting and food) *in vivo* bioequivalence studies comparing its 75 mg ketoprofen capsules with Wyeth-Ayerst's Orudis^R 75 mg capsules (submission date 1/10/91, Division of Bioequivalence date 8/19/91, reviewed by B. Chen).

The fasting study was found unacceptable due to the rate of absorption (Cmax) failed to meet the required confidence intervals.

II. Introduction:

Ketoprofen, a nonsteroidal antiinflammatory drug, is used for the treatment of rheumatoid arthritis and osteoarthritis. The following information is taken from Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 1990, American Hospital formulary Service, *AHFS 90*, and *Physicians' Desk Reference, PDR 1992*:

Absorption	• Rapid and complete oral absorption (absolute bioavailability ≈ 90%) • Food and milk (with a 50 mg dose) decreases the mean C_{max} from 4.1 ug/mL to 2.4 ug/mL, delays the T_{max} from 1.1 hr to 2.0 hr, but not affect the AUC.
Distribution	• To body fluids and tissues with an apparent volume of distribution (V_d) of 0.1 L/kg • Extensively bound to plasma proteins (99%, mainly to albumin)

Metabolism	• Inactive hydroxylated metabolites and their glucuronides (liver)
Elimination	• Biphasic declination (terminal $T_{1/2} \approx 2$ hrs); slightly longer half-life in elderly subjects • 50-90% of oral dose in urine (≤1% unchanged drug) and 1-8% in feces in 1-5 days
Dosing/Dosage form	• Initial daily dose for rheumatoid arthritis = 75 mg t.i.d. or 50 mg q.i.d. • Capsule, 25 mg, 50 mg and 75 mg

III. Review of the Protocol: Study No. KETO-9119

A. Study Center and Investigators:

Clinical and Analytical Site:

Clinical Investigator:
Analytical Investigat

B. Study Design:

A single dose, randomized, two-way crossover bioequivalence study under fasting condition

Treatment Drugs: Each dose will be composed of one 75 mg capsule of the following products with 240 mL of water.

Test Product: Mylan's Ketoprofen 75 mg Capsules
Reference Product: Wyeth Ayerst's Orudis^R 75 mg Capsules

Subject Requirements:

Forty healthy male volunteers between 19 and 55 years of age, weighed within 10% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983), judged healthy based on medical history, physical examination, ECG, and clinical laboratory findings (hematology, serum chemistry, urinalysis, and liver function tests including protein and albumin levels) will be selected.

Each subject will sign a written informed consent form.

Exclusion Criteria:

Subjects with the following conditions will be excluded:

- who has received an investigational drug within 4 weeks prior to the study
- who smokes tobacco
- who has an acute illness or surgery 4 weeks prior to the study
- who has allergic response to aspirin, ketoprofen or other NSAID drugs
- who is an alcohol or drug abuser within the past year
- who is sick with G-I tract, renal, cardiac, diabetes, psychosis, glaucoma, or hyperthyroidism
- who takes any medications (including OTCs) within fourteen days prior to the study
- who has a history of using psychotropic agents or the presence of cardiac arrhythmias

Procedures:

Following a ten hours fast at the clinical study site, the subjects will be administered the treatment dose and kept ambulatory in the study center for at least 24 hours.

Standard meals will be served throughout the study phase. No xanthine-containing beverages will be allowed during the confinement period (-10 hours to 24 hours). After lunch (at 4 hours after dosing), decaffeinated fluids will be allowed ad lib.

Blood Sampling:

Blood samples (10 mL) will be taken at the following time: predose, 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours (19 samples per period). Plasma samples will be immediately separated and frozen at ≤ 20°C until analysis.

No urine samples will be collected.

Washout Period: ≥ One week

C. Analytical Methodology:

D. Data Analysis:

Various pharmacokinetic parameters (e.g. $AUC_{0-24\,hr}$, AUCinf, C_{max}, T_{max}, Kel, $T_{1/2}$ derived from the plasma ketoprofen data) will be compared for the bioequivalence evaluation. Statistical analyses will be performed to assess drug, sequence and period effects using ANOVA. The 90% confidence intervals (the two one-sided tests procedure) will be calculated.

E. Clinical Adverse Reactions:

All clinical complaints will be reported and evaluated by whether they are drug related.

IV. Comments:

1. As the firm indicated, the validation of the analytical method will include sensitivity, specificity, linearity, and recovery. It is important that one should also include accuracy, precision and stability.

   The stability of the samples should cover the following conditions:

   The firm should make sure that QC and standard samples will be stored along with the study samples.

2. Information on the standard curves should be provided. In addition, if a weighting scheme is used in the construction of the standard curves, justification should be given to explain the selection.

3. For the test product, if a new formulation is used (as compared to the formulation used in previous submission), a food study should be conducted. A three-way cross over design is recommended. The meal prior to dosing should be composed of the following:

   one fried egg
   one buttered English muffin
   one slice of Canadian bacon
   one slice of American cheese
   one serving of hash brown potatoes
   six ounces (180 mL) of orange juice
   eight ounces (240 mL) of whole milk

The batch size should be capsules and the potency of the test product should be ≤± 5% of the reference product. The dissolution testing and the formulation should be provided in the final report.

4. The firm should estimate $AUC_{0\text{-last}}$ instead of $AUC_{0\text{-24 hr}}$.

5. For Kel estimation, the firm should indicate the data points used in each individual's calculation, along with the explanations for selecting those points and goodness of fit data.

6. For adverse reaction report, the firm should indicate the type of the product taken (test or reference) prior to the occurrence of the adverse effects.

7. It is suggested that the subjects be between 20 - 40 years of age instead of 19 - 55.

8. There are two minor errors in this protocol:

   (1) In the cover letter, the word tolmetin should be corrected to mean ketoprofen, and

   (2) On p.7, total blood volume of 170 mL should be changed to 190 mL during each phase of blood collection.

V. Recommendation:

The protocol for a proposed bioequivalence study comparing Mylan's ketoprofen 75 mg capsule with Wyeth-Ayerst's Orudis^R 75 mg capsules is acceptable provided the firm incorporates the Comments in the revised protocol.

Beatrice P. Chen

Beatrice P. Chen, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALLED FPELSOR
FT INITIALLED FPELSOR 6-9

Concur: Shrikant V. Dighe Date: 6/9/92

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

BPC/6-9-92/74035P.592

acc: ANDA # 74-035 original, HFD-604 (Hare), HFD-630, HFC-130 (JAllen), HFD-655 (Pelsor, BChen), Drug File

AUG 19 1991

Ketoprofen Capsules
50 mg and 75 mg
ANDA # 74-035
Reviewer: Beatrice P. Chen
74035SDW.191

Mylan Pharmaceuticals Inc.
Morgantown, West Virginia
Submission Date:
January 10, 1991

Review Of Two In-Vivo Bioequivalence Studies (Under Fasting and Non-fasting Conditions) And Two Waiver Requests

I. Objective:

The firm has submitted two in vivo bioequivalence studies comparing its 75 mg Ketoprofen capsules with Wyeth-Ayerst's Orudis^{R} 75 mg capsules administered under fasting and food conditions for approval. The firm has also requested waivers of in vivo bioequivalence study requirements for its 50 mg and Ketoprofen capsules.

II. Introduction:

Ketoprofen is a nonsteroidal antiinflammatory drug used in the treatment of rheumatoid arthritis and osteoarthritis. It has the chemical name of 2-(3-benzoyl-phenyl)-propionic acid and a pKa of 5.9. It probably acts by reversibly inhibition of cyclooxygenase and lipoxygenase which involved in the synthesis of prostaglandin and leukotrienes.

Ketoprofen is rapidly and completely absorbed from the G-I tract with an absolute bioavailability of 90%. Oral doses of 50 mg, 100 mg, and 150 mg yield linear Cmax levels of 3.2-4.8 ug/mL, 5.5-10.1 ug/mL, and 13.1 ug/mL, respectively. Food and milk together with a 50 mg dose decreases the mean C_{max} from 4.1 ug/mL to 2.4 ug/mL, and delays the T_{max} from 1.1 hr to 2.0 hr, but not affect the AUC.

Following absorption, ketoprofen is distributed into body fluids and tissues, such as synovial fluid and CNS with an apparant volume of distribution (V_d) of 0.1 L/kg. Patients with alcoholic cirrhosis appear to have increased V_d.

Plasma ketoprofen is 99% bound to proteins, mainly albumin. It declines in a biphasic manner with a terminal $T_{1/2}$ of 1.1 to 4 hrs. It is converted to the inactive hydroxylated metabolites and their glucuronides in the liver. About 50-90% of dose is excreted in the urine (with less than 1% as unchanged drug) and 1-8% in feces within 1-5 days.

Ketoprofen is marketed only in the form of capsule 50 mg and 75 mg). The initial dose for rheumatoid arthritis is 75 mg three times daily or 50 mg four times daily. Reduced dosage is recommended for pain relief and in renal impaired patients.

III. Study Center and Investigators:

Clinical Site:

Clinical Investigator:

Analytical Site: Mylan Pharmaceuticals Inc., Morgantown, WV

Analytical Investigator: Patrick K. Noonan, Ph.D.
Director of Pharmacokinetics

IV. In-Vivo Bioequivalence Studies:

Two studies were conducted with one under Fasting and the other under Non-fasting conditions.

A. Fasting Study: Study No. KETO-8918, 10/15/89 - 10/23/89
B. Non-Fasting Study: Study No. KETO-8921, 10/29/89 - 11/06/89

V. Study Design:

Each study was a single dose, randomized, two-way crossover bioequivalence study.

Treatment Drugs: Each dose composed of one 75 mg capsule of the following products with 240 mL of water.

Test Product: Mylan's Ketoprofen 75 mg Capsules
lot # 2T007G (lot size, otency 99.3%)

Reference Product: Wyeth Ayerst's Orudis^{R} 75 mg Capsules
lot # 9880396 (exp. date 09/91, potency 99.4%)

Subject Requirements:

Male volunteers (26 for Fasting study and 20 of that same group continued for Non-fasting study) between 19 and 36 years of age, and weighed within 10% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983) and were judged healthy based on medical history, physical examination, ECG, and clinical laboratory findings (hematology, serum chemistry, urinalysis, and liver function tests).

Each subject signed a written informed consent form.

Exclusion Criteria: Subjects with the following conditions were excluded:

- who had received an investigational drug within 4 weeks prior to the study
- who smokes tobacco
- who had an acute illness or surgery 4 weeks prior to the study
- who had allergic response to aspirin, ketoprofen or other NSAID drugs
- who was an alcohol or drug abuser
- who was sick with G-I tract, renal, cardiac, diabetes, psychosis, glaucoma, or hyperthyroidism

Restrictions:

- participated in a clinical trial within the past 4 weeks
- taken any medications (including OTCs) within fourteen days prior to the study

Procedures:

For Fasting study, following a ten hours fast at the clinical study site, the subjects were administered the treatment dose and were kept ambulatory and remained in the study center for at least 24 hours.

For the non-fasting study, following an overnight fast, at 30 minutes prior to each treatment dose, the subjects were administered the following standard high-fat breakfast which should be taken in 15 minutes:

8 ounces of whole milk
2 scrambled eggs
2 strips of bacon
2 slices of toast with butter
2-4 ounces of hash brown potatoes

Standard meals were served throughout the study phase. Alcohol, caffeine and xanthine-containing beverages were restricted during the confinement period (-10 hours to 24 hours). After lunch (at 4 hours after dosing), decaffeinated fluids were allowed ad lib.

Blood Sampling:

An indwelling catheter was placed in a forearm antecubital vein. Blood samples (10 mL) were taken at the following time: predose, 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours (19 samples per period). Plasma samples were immediately separated after centrifugation and frozen until analysis.

Urine Samples:

Urine samples at the indicated time intervals (-1-0, 0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours post-dose) were collected. After measuring the volume and pH, aliquots were frozen for possible analysis.

Washout Period: One week

VI. **Analytical Methodology**: (listed under each study)

VII. **Data Analysis**:

Pharmacokinetic parameters, AUC_{0-t}, AUCinf, C_{max}, T_{max}, Kel, $T_{1/2}$ were derived from the plasma ketoprofen data. Those parameters were analyzed by SAS using GLM procedure for analysis of variance (ANOVA) to determine statistically significant ($p < 0.05$) differences between treatment, sequence and period effects of the test and reference products. The 90% confidence intervals (the two one-sided tests procedure) were calculated for the major pharmacokinetic parameters for both fasting and non-fasting studies.

The firm also conducted log transformation of Cmax for the fasting study.

A. Fasting Study

Study dates: Oct. 15, 1989 - Oct. 23, 1989
Study No. Keto-8918

Subjects:

Twenty-six (26) male volunteers started and completed the study.

Analytical Methodology: (Not to be released under FOI)

Clinical Complaints:

One volunteer complained of a slight swelling of the upper lip at one hour post dose which lasted about one hour.

Study Results:

All 26 subjects samples (26 x 19 x 2 = 988) were analyzed and 61 samples (6%) were reassayd.

The reassays and the final data are reasonable. Among the reassays, 64% used the mean of original and reassay readings, 31% used single reassay values, 3% used the duplicate reassays, and 2% used the original data.

The plasma levels (Table I, and Fig. I, attached) and their derived pharmacokinetic parameters (Table II) are summarized below:

Table I Fasting Study (n=26)
Mean Plasma Ketoprofen Levels and Pharmacokinetic Parameters
Following An Oral Dose of Ketoprofen Sodium 550 mg Tablet

Test Product: Mylan's Ketoprofen 75 mg Capsules, lot # 2T007G

Reference Product: Wyeth Ayerst's Orudis^{R} 75 mg Capsules lot # 9880396

Time	Test		Reference	
hr	ug/mL	(%CV)	ug/mL	(%CV)
0	0.00	-	0.00	-
0.17	0.02	300	0.00	-
0.33	2.62	68	0.96	92
0.5	4.67	57	3.52	70
0.75	5.14	53	5.77	55
1	4.67	44	5.68	98
1.25	4.08	36	5.04	34
1.5	3.70	35	4.29	33
2	2.98	35	3.14	25
3	1.79	37	1.69	34
4	1.06	45	0.93	27
5	0.59	39	0.61	49
6	0.37	35	0.37	43
7	0.22	32	0.23	39
8	0.14	50	0.18	78
10	0.04	150	0.06	217
12	0.02	250	0.02	400
16	0.00	-	0.01	300
24	0.00	-	0.00	-

		T (%CV)		R (%CV)		T/R	90% C.I.
AUC_{0-T} ug-hr/mL	12.75	(19)	13.02	(19)	0.98	93.0-102.8%
AUCinf ug-hr/mL	13.04	(19)	13.34	(19)	0.98	93.2-102.4%
Cmax ug/mL	6.19	(39)	7.06	(33)	0.88	74.8-100.5%
log Cmax ug/mL	1.741	(25)	1.883	(23)	0.92	73.6-102.1%
Tmax,hr	1.096	(59)	1.010	(43)	1.09	86.3-129.5%
Kel, hr^{-1}	0.424	(21)	0.423	(19)	1.00	
K1/2, hr	1.717	(25)	1.709	(23)	1.00	

*Confidence Interval calculations were based on least squares means.

All 26 subject's data were used for statistical analysis. The mean difference between the test and the reference products in AUC_{0-t} and AUCinf were both 2%, and the 90% confidence intervals (C.I.) were both 93-102% and acceptable. ANOVA showed no statistically significant treatment effect, sequence effect, or period effect for AUCs and Cmax.

The mean difference for Cmax was 12% and the 90% C.I. was 75 - 100%. The firm showed that C_{max} data were not normally distributed and calculated the log transformed Cmax which they reported to be 84 - 101% and acceptable. The reviewer justified the used of log transformation with the Box-Cox test, but found, however, the 90% C.I. was 74 - 102%, still outside of the 80 - 120% range.

Therefore, C_{max} failed the 90% C.I. by exceeding the lower limit of the allowed equivalence interval.

B. Non-fasting Study

Study dates: Oct. 29, 1989 - Nov. 6, 1989
Study No. Keto-8921

Subjects: Twenty out of the 26 subjects who were employed for the fasting study started and completed the study.

Clinical Complaint: No clinical complaints were reported.

Analytical Methodology: (Same as those listed under Fasting study except the following)

see

Results:

The study was completely balanced and 20 subjects' samples (20 x 19 x 2 = 760) were assayed. Of which 45 samples (6%) were reassayed and the final data used the mean of original and reassayed values (76%) or the reassayed (duplicate and single repeats) (24%). The reassays and the final reported data are reasonable.

The plasma levels (Table II, and Figure II attached) and their derived pharmacokinetic parameters are summarized below:

Table II Non-Fasting Study

Mean Plasma Ketoprofen Levels and Pharmacokinetic Parameters Following An Oral Dose of Ketoprofen 75 mg Capsule (n=20)

Test Product: Mylan's Ketoprofen 75 mg Capsules, lot # 2T007G

Reference Product: Wyeth Ayerst's Orudis^{R} 75 mg Capsules lot # 9880396

Time	Test		Reference	
hr	ug/mL	(%CV)	ug/mL	(%CV)
0	0.00	-	0.00	-
0.17	0.01	(200)	0.35	(440)
0.33	0.37	(138)	0.57	(346)
0.5	0.65	(117)	0.70	(266)
0.75	0.88	(131)	0.82	(179)
1	0.97	(116)	0.95	(133)

1.25	1.21	(83)	1.07	(96)	
1.5	1.45	(59)	1.26	(67)	
2	1.74	(39)	1.60	(41)	
3	1.74	(34)	2.12	(40)	
4	1.82	(37)	2.18	(36)	
5	1.22	(42)	1.32	(32)	
6	0.82	(70)	0.79	(44)	
7	0.52	(67)	0.48	(48)	
8	0.37	(73)	0.31	(35)	
10	0.31	(106)	0.23	(87)	
12	0.09	(144)	0.07	(186)	
16	0.01	(500)	0.01	(400)	
24	0.00	-	0.00	-	

	T (%CV)		R (%CV)		T/R	90% C.I.
AUC_{0-T} ug-hr/mL	10.04	(17)	10.42	(15)	0.96	93.6-101.2%
AUCinf ug-hr/mL	10.61	(17)	10.82	(15)	0.98	93.0-103.1%
Cmax ug/mL*	2.47	(32)	2.94	(52)	0.84	63.4-104.7%
$Cmax_{ug/mL}^{-1}$	2.44	(33)	2.62	(24)	0.93	77.4-107.8%
Kel hr	0.3706	(24)	0.3987	(24)	0.93	84.0-101.9%
T1/2, hr	2.16	(66)	1.85	(29)	1.17	
Tmax, hr	3.41	(60)	3.17	(41)	1.08	

*Calculations based on least squares means.

This food study (n=20) showed a similar mean plasma profiles of the test and the reference products with a broad peak around 2-4 hours (Table II and Figure II). The mean test to reference ratios of AUC_{0-T}, AUCinf, and Cmax were 0.96, 0.98, and 0.84, respectively.

Since the fasting study did not demonstrate bioequivalence for the test product, the 90% C.I. in this study was evaluated. The 90% C.I. of the AUCs were within 91 to 103%, and ANOVA showed no statistically significant treatment, sequence, or period effects for AUCs and Cmax. However, the 90% C.I. for Cmax was 63.4 - 104.7%, outside of 80 - 120% range. The firm deleted one subject (considered him as an outlier) and recalculated the C.I., which became 77.4% - 107.8% and was still outside of the 80% lower limit.

The reviewer did a SAS analysis using data from all subjects for log transformed Cmax. The Box Cox test did not support the use of log transformation, and the 90% C.I. for the log Cmax was 74.2 - 101.8%, still outside of the ±20% limit.

VIII. Comparison of Fasting Versus Non-fasting Studies:

The present two studies (fasting and food) indicate the following (in spite of the difference in the number of subjects and not being conducted at the same time):

> Food significantly decreased the Cmax (about 245%, 6.6 to 2.7 ug/mL), and significantly delayed the Tmax (from 1 hour to 2-3 hours), and much less affected the AUCs (about 24%, 13 to 10.4 ug-hr/mL). These observations are similar to those in the literature that food reduce the rate but not the extent of ketoprofen absorption (Goodman and Gilman's Pharmacological Basis of Therapeutics, 8th Edition, p.667, 1990).

IX. Dissolution Testing: (Please see Table III attached)

Condition: The medium was 1000 mL of 0.05 M phosphate buffer pH 7.4 at 37^0C, and the apparatus was USP XXII apparatus II (paddle) at 50 rpm.

Specifications: NLT dissolved in 45 minutes.

Products Tested:

Test Product: Mylan's Ketoprofen Capsules
75 mg, lot #2T007G (size
50 mg, lot #2T006G (size

Reference Product: Wyeth Ayerst's Orudis^R Capsules
75 mg, lot # 9880396;
50 mg, lot # 9890021;
25 mg, lot # 9900309

X. Formulations:

The firm's comparative compositions are listed below:

	PER CAPSULE MG	MG
ACTIVE COMPONENT		
Ketoprofen	50.0	75.0
INACTIVE COMPONENTS		
Microcrystalline Cellulose, NF		
Magnesium Stearate/Sodium		
Colloidal Silicon Dioxide, NF		
Croscarmellose Sodium, NF		
Lactose Fast Flo (Hydrous), NF		

XI. Comments:

1. The validation of the analytical method is acceptable. The sensitivity, specificity, linearity, precision and accuracy for both studies were demonstrated, and the coefficients of variation for standard samples and three quality control samples (0.5, 2.5, and 10 ug/mL) were within ±10% of the theoretical values. The stability of the samples during storage and reinjection is also acceptable.

2. Mylan's in vivo bioequivalence studies on its Ketoprofen 75 mgcapsules, 75 mg Capsules, lot # 2T007G, comparing with Wyeth Ayerst's Orudis^{R} 75 mg Capsules demonstrated a comparable AUC with mean difference of -2% and 90% confidence interval of 93 - 103% under both fasting and non-fasting conditions.

   In fasting study (n=26), the mean Cmax for the test product was 12% lower than the reference product and the 90% confidence interval was 74.8 - 100.5% for the untransformed data and 73.6 - 102.1% for log transformed data. They were 5-6% outside of the lower acceptable limit of 80%. The mean Tmax was 9% larger for the test product. In non-fasting study (n=20), the mean Cmax was -16% lower, and the 90% confidence interval was 63.4 - 104.7%. Even after the firm deleted one subject as "outlier", the 90% C.I. was still only 77.4-107.8%, outside of the lower 80% limit.

Whether the test product with a lower Cmax can be considered therapeutically equivalent and to accept the in vivo fasting study requires the consultation of an appropriate medical officer.

3. In the food study, the mean ratios of the AUC_{0-T} (0.96), AUCinf (0.98), and Cmax (0.84) were within ±20% to each other. Since the Cmax for the fasting study was outside of the ±20% of the 90% C.I., the food study is further evaluated and the 90% C.I. for Cmax was found to be 63 - 104%. The firm deleted one subject (considering him to be an outlier) and the resultant 90% C.I. was 77% - 108%, still outside of the lower limit of 80%.

4. The in vitro dissolution testing and the formulation proportionality for the test products 50 mg, and 75 mg capsules meet the Agency's requirements. However, the final decision on their acceptance and granting the waivers of bioequivalence studies awaits an acceptable in vivo bioequivalence study of the 75 mg capsule.

5. The concentration of the dissolution medium was reported to be 0.1M (Vol. 1.3, the waiver request section) which was in fact 0.05 M (based on the amount described on p.458, Vol. 1.1). The 0.05 M is the Agency specified concentration.

XII. Deficiencies:

1. In the fasting study, the confidence interval for Cmax is outside of the lower acceptable limit of 80 - 120%.

2. There is a major error in the firm's calculation for the 90% confidence interval for its log transformed Cmax. The firm's calculation of 84% - 101% (p.86) should be corrected to 73.6% - 102.1% which resulted the 90% confidence interval being outside of the allowable ±20% range.

XIII. Recommendations:

1. The in vivo bioequivalence study under fasting condition conducted by Mylan Pharmaceuticals, Inc. on its Ketoprofen 75 mg Capsules, lot # 2T007G, comparing them to Orudis^R 75 mg Capsules manufactured by Wyeth-Ayerst has been found unacceptable to the Division of Bioequivalence (Please see the Deficiencies).

2. The recommendation on the in vivo bioequivalence study under non-fasting condition will not be made because of the unacceptability of the fasting study.

3. The in vitro dissolution testing conducted by Mylan Pharmaceutical, Inc. on its Ketoprofen 75 mg Capsules, lot # 2T007G comparing with Wyeth Ayerst's Orudis^R 75 mg Capsules is acknowledged.

4. The recommendation to grant the waivers of in vivo bioequivalence study requirements for the 50 mg, and capsules of the test product is pending the acceptance of the in vivo bioequivalence studies of the 75 mg capsules.

Beatrice P. Chen

Beatrice P. Chen, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALLED FPELSOR
FT INITIALLED FPELSOR

Concur: Shrikant V. Dighe Date: 8/16/91.

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

BPC/stm/8-13-91/74035SDW.191

cc: ANDA # 74-035 original, HFD-600 (OGD), HFD-604 (Hare), HFD-630, [redacted] ([redacted]), HFC-130 (JAllen), HFD-655 (Pelsor, BChen), Drug File

FIGURE 1. MEAN KETOPROFEN CONCENTRATION VS. TIME PROFILE

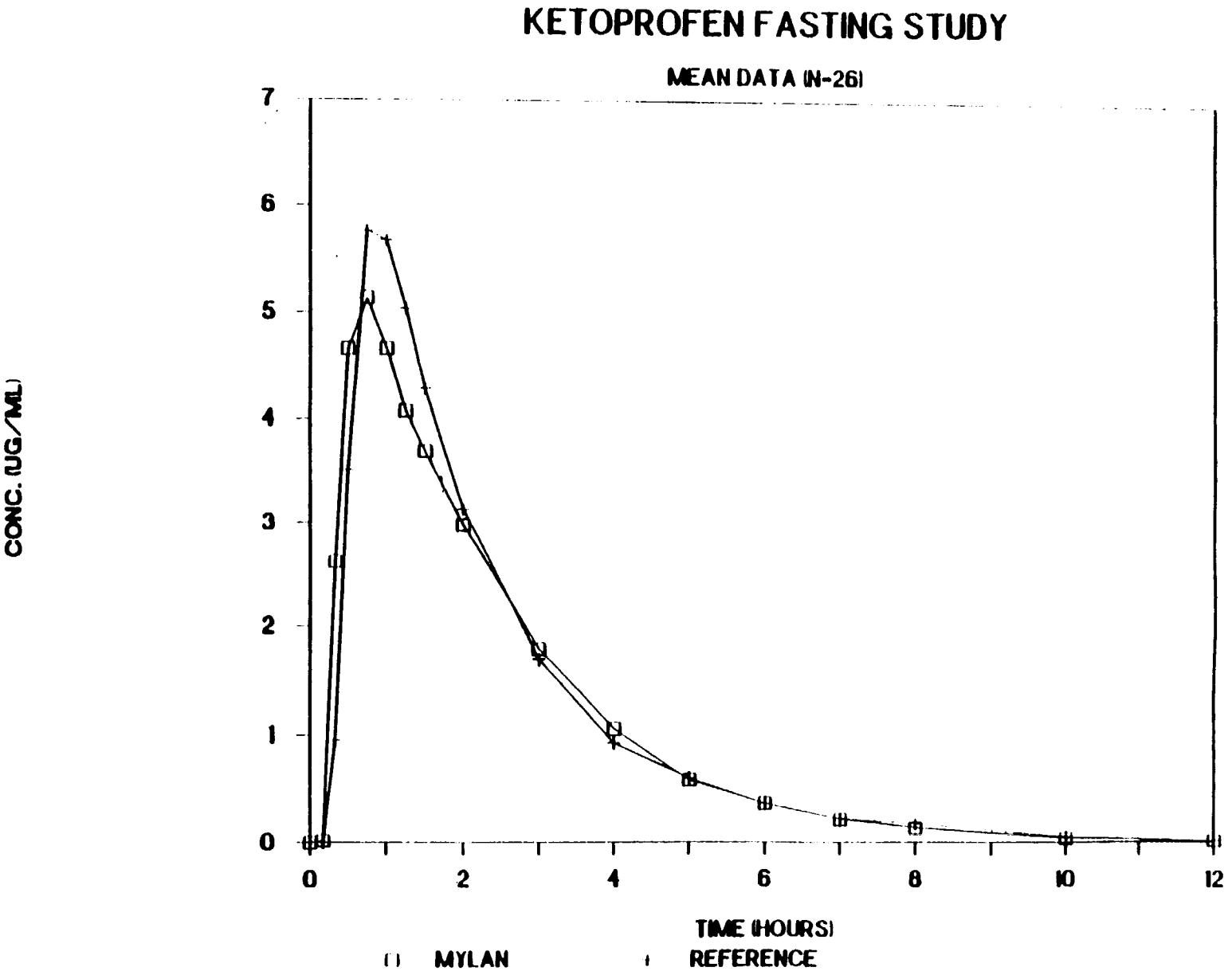
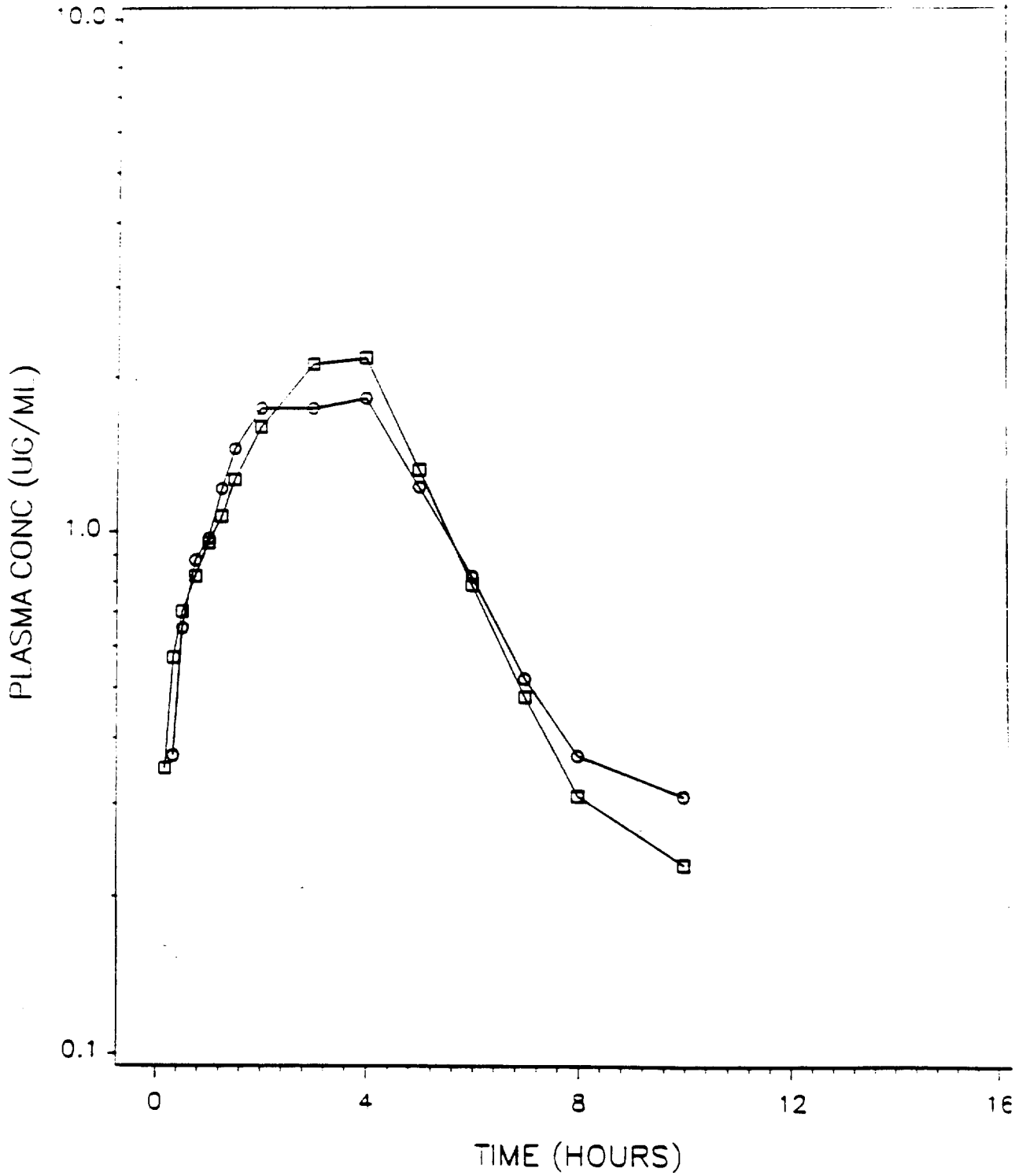


Figure II

KETOPROFEN FOOD STUDY

PROTOCOL KETO-8921

MEAN PLASMA CONCENTRATIONS (N=20)



DIV

ANDA 74-035

Mylan Pharmaceuticals Inc.
Attention: Patrick K. Noonan, Ph.D.
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown WV 26504-4310

FEB 12 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ketoprofen Capsules 75 mg and 50 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs.

   The dissolution testing should be conducted in 1000 mL of pH 7.4, 0.05M Potassium Phosphate Buffer at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 2 1996

Ketoprofen
75 mg and 50 mg Capsule
ANDA 74-035
Reviewer: Pradeep M. Sathe, Ph.D.
WP #74035SDW.595

Mylan Labs
Morgantown, WV-26504
Submission Date:
May 23, 1995
July 5, 1995

REVIEW OF BIO-STUDIES, DISSOLUTION AND A BIO-STUDY WAIVER REQUEST

I.INTRODUCTION : Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID). It's chemical name is 2-(3-benzoylphenyl)-propionic acid. The molecular formula is $C_{16}H_{14}O_3$ which relates to a molecular weight of 254.29. It is a white/off white powder with a melting point about 95°C.

The drug is rapidly and completely absorbed from the G.I. tract. Mean peak plasma levels are reached in 0.5 to 2.0hr. The plasma clearance is approximately 0.08 L/kg/hr with a Vd of 0.1 L/Kg. The absolute bioavailability after oral administration is about 90% and half-life is about 2-4hr.

Currently, there are two other Ketoprofen capsule formulations on the market besides Wyeth-Ayerst's Orudis^R, which is the reference formulation.

The "Clinical Pharmacology" section of Orudis^R labelling states that "When ketoprofen is administered with food, its total bioavailability is not altered, however, the rate of absorption is slowed resulting in delayed and reduced peak concentrations Cmax". The "Dosage and Administration" of the labelling recommends a dose of 150-300 mg to be taken in three to four doses. In the same section it states that "As with other NSAID drugs, the predominant adverse effects of ketoprofen are gastrointestinal. To attempt to minimize these effects, physicians may wish to prescribe that Orudis be taken with Antacids, food or milk".

II.CURRENT SUBMISSION : The current application consists of a single dose A] fasting bio-equivalency study comparing 75 mg test (Mylan's Ketoprofen) and reference (Wyeth Ayerst's Orudis^R) capsule formulations, B] "food challenge" bio-equivalency study comparing 75 mg test (Mylan's Ketoprofen) and reference (Wyeth Ayerst's Orudis^R) capsule formulations, C] dissolution methodology and data comparing the 75 mg and 50 mg test and reference formulations and D] bio-study waiver requests for the 50 mg strength test formulation.

III.BACKGROUND : The firm had originally submitted bioequivalence studies for 75 mg strength Ketoprofen capsule formulation, total capsule weight 250 mg on January 10, 1991. The application was found unacceptable by the Agency. Since then the firm has modified its Ketoprofen capsule formulation to contain active

ingredient and qualitatively and quantitatively different inactives. The new 75 mg strength formulation has a total weight of 300 mg. The comparative formulation data for the old and new formulations are given in Attachment I.

IV.TEST FORMULATIONS : The 75 mg and 50 mg test formulation compositions are as follows:

Active Component	**50 mg Strength**	**Percent**	**75 mg Strength**	**Percent**
Ketoprofen	50 mg	16.7	75 mg	25.0
Inactive Components				
Lactose Monohydrate				
Sodium Starch Glycolate				
Sodium Lauryl Sulfate				
Colloidal Silicon Dioxide				
Starch				
Magnesium Stearate/Sodium Lauryl Sulfate				
Total Theoretical Weight	**300.0 mg**	**100.0**	**300.0 mg**	**100.0**

Ketoprofen is the active ingredient. Lactose is the diluent, sodium starch glycolate is a pharmaceutical aid, sodium lauryl sulfate is a surfactant, colloidal silicon dioxide is suspending/thickening agent, starch is disintegrant and magnesium stearate/sodium lauryl sulfate is a lubricant. The two formulations are adjusted for a constant weight. Except lactose, all inactives are also adjusted to a constant percentage weight. The lactose percent difference for the two formulations accounts for the percent difference in active moiety weight.

V.BIO-STUDY NO.KETO-9412, FASTING BIOEQUIVALENCY STUDY :

A. TITLE : Single dose bioequivalence investigation comparing Mylan Ketoprofen capsules (75 mg) with Orudis^{R} (Wyeth-Ayerst) capsules (75 mg)

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY :

1. Clinical Investigator :

2. Bio-Study Site :

3. Analytical Investigator : Patrick K. Noonan, Ph.D.

4. Study Sponsor : Mylan Pharmaceuticals, Inc.
P.O. Box 4310,
Morgantown, West Virginia 26504

C. STUDY OBJECTIVE : To compare the oral absorption and elimination of two formulations of ketoprofen capsules following administration of a 75 mg dose under fasting conditions.

D. STUDY DESIGN AND NUMBER OF SUBJECTS : This was a randomized two treatment, single dose crossover design with a two week washout period between the two study phases. A total of 40 subjects were recruited for the study. Seven subjects did not report for the trial and the firm decided to complete the study with 33 subjects. All thirty-three (33) subjects completed both phases of the study.

E. SUBJECT SELECTION/EXCLUSION CRITERIA : Volunteers were selected in the study if they met the following criteria:

1. Males between the ages of 21 and 40 years, inclusive.
2. Physical examination and medical history within normal limits.
3. Within ±10% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983).
4. Normal electrocardiogram
5. Laboratory evaluations are not to exceed 10% of normal limits (with exception of parameters that are not clinically relevant, e.g. cholesterol). These tests should include:

a) Complete blood count, differential and platelets.
b) Electrolytes: sodium, potassium, chloride, calcium and phosphorous.
c) Liver function tests: SGOT, SGPT, alkaline phosphatase, total bilirubin, total protein and albumin.
d) Kidney function tests: BUN, serum creatinine.
e) Other blood tests: Uric acid, cholesterol, iron.
f) Urinalysis, urine drug screen.
g) Laboratory results not within ±10% of normal range (except cholesterol and triglycerides) should be repeated, then the investigator should judge whether they are clinically significant.
6. Physical exam, ECG and laboratory tests should be conducted within 2 weeks of the study.

Volunteers were excluded from the study if they had the following:

1. Any subject who has received the investigational drug within

four weeks prior to entry into the study.
2. Any subject who uses tobacco in any form.
3. Any subject who had an acute illness or surgery during the four weeks prior to entry into the study.
4. History of adverse reactions or allergy to aspirin, ketoprofen or other non-steroidal anti-inflammatory drugs.
5. History of past or recent alcohol or drug addiction or abuse.
6. History or presence of significant systemic or organ disease including, but not limited to, renal, cardiovascular, hepatic, hematopoietic, neurological (including epilepsy), pulmonary (including bronchial asthma, tuberculosis and allergic rhinitis) or gastrointestinal pathology.
7. Presence of psychiatric disorders, glaucoma, diabetes or hyperthyroidism.
8. Any other medications (including OTC) within 14 days prior to the start of the study.
9. Ingestion of alcoholic beverages or caffeine- or xanthine-containing foods or beverages within 48 hours prior to start of the study.
10. History of use of psychotropic agents.
11. History of presence of cardiac arrhythmias.
12. Blood donation within 30 days prior to the study.
13. Exposure to known hepatic enzyme inducing or inhibiting agents within 30 days prior to the study.

F. SUBJECT RESTRICTIONS : The following restrictions were put on the subjects throughout the study:

1. No concurrent medication other than the study drug.
2. No caffeine or xanthine-containing foods and beverages.

G. STUDY SCHEDULES :

1. **Methods** : Each treatment consisted of administration of either the test or reference formulation (1*75 mg) with 240 ml water following a 10 hr fast. Standard meals were served at 4 and 10 hr after the dose. Liquids were not allowed from one hour before until one hour after dosing. Blood samples were drawn as per the blood sampling schedule.

2. **Randomization Schedule** :

Treatment Phase I	Phase II	Volunteer Number
A	B	1, 4, 6, 8, 9, 11, 14, 15, 18, 19, 21, 23, 26, 28, 29, 32, 33
B	A	2, 3, 5, 7, 10, 12, 13, 16, 17, 20, 22, 24, 25, 27, 30, 31

3. **Blood Sampling** : Serial blood samples were collected at 0hr

(pre-dose), 0.17, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24hr after dosing. The blood samples were collected in heparinized Vacutainers. Plasma samples were separated and stored at -20^{0}C in the acidified (40% citric acid) vials until analysis.

H. DRUG TREATMENTS :

1. TEST PRODUCT A : Ketoprofen Capsule, 1*75 mg (Mylan Labs.), Lot # 2A002H, Assay Potency=97.0%, Batch Size

2. REFERENCE PRODUCT B : Orudis^R Capsule, 1*75mg (Wyeth-Ayerst), Lot # 9930192, Assay Potency=99.1%, Expiry date: 01/96

I. ASSAY METHODOLOGY : **The following assay methodology may be a proprietary information of the firm and therefore should not be released under F.O.I.**

J. PHARMACOKINETICS AND STATISTICS : The pharmacokinetic parameters such as area under the curve until the last measurable sample point, AUC_t, area under the curve until the infinite time, AUC_{inf}, maximum observed concentration, Cmax, time of observed maximum concentration Tmax and half-life $T_{1/2}$ were evaluated. The parameters were analyzed using analysis of variance in SAS. The bioequivalence of the mean parameters was assessed using a two one sided t-test procedure.

K. RESULTS OF THE BIOEQUIVALENCY STUDY : The mean plasma concentration time data for the test and the reference formulations are given in Table 1.1. The mean pharmacokinetic parameters and 90% confidence intervals are listed in Table 1.2. The mean plasma concentration time profiles are given in Attachment 1.3. The plasma levels are expressed as microgram/ml, AUC as (microgram/ml)*hr, and Tmax and half-life as hours.

Table 1.1 : Ketoprofen plasma level (ug/ml) data, N=33, (Mean±SE)

Time (hr)	Mylan (Test)	Wyeth-Ayerst (Reference)
0.0	0.0 (0.0)	0.0 (0.0)
0.17	0.13 (0.03)	0.07 (0.05)
0.33	2.77 (0.41)	2.42 (0.48)
0.5	4.91 (0.43)	4.62 (0.57)
0.75	5.43 (0.36)	5.19 (0.44)
1.0	4.65 (0.25)	4.48 (0.31)
1.25	4.09 (0.20)	3.80 (0.22)
1.5	3.53 (0.17)	3.46 (0.20)
2.0	2.69 (0.12)	2.80 (0.17)
3.0	1.49 (0.11)	1.68 (0.11)
4.0	0.90 (0.06)	1.03 (0.10)
5.0	0.53 (0.03)	0.57 (0.04)
6.0	0.31 (0.02)	0.33 (0.02)
7.0	0.20 (0.01)	0.20 (0.01)
8.0	0.11 (0.01)	0.13 (0.01)
10.0	0.02 (0.01)	0.03 (0.01)
12.0	0.00 (0.0)	0.0 (0.0)
16.0	0.00 (0.0)	0.0 (0.0)
24.0	0.00 (0.0)	0.0 (0.0)

Table 1.2 : Mean Pharmacokinetic Parameters ± SD, N=33

PK Parameter	Mylan (Test)	Wyeth-Ayerst (Reference)	T/R ratio	90% Con.Int.
AUC_t	11.91 (1.74)	12.08 (2.12)	0.98	95-102
$LnAUC_t$	2.47 (0.15)	2.48 (0.18)	0.99*	96-102
AUC_{inf}	12.28 (1.77)	12.43 (2.17)	0.98	95-102
$LnAUC_{inf}$	2.50 (0.15)	2.51 (0.18)	0.99*	96-102
Cmax	6.22 (1.99)	6.49 (2.61)	0.96	81-110
LnCmax	1.78 (0.33)	1.79 (0.41)	0.99*	85-114
Tmax	0.84 (0.52)	1.06 (0.74)		-----
$T_{1/2}$	1.87 (0.75)	1.80 (0.57)		-----

* = Ratio of antilogs of geometric means

L. ADVERSE EFFECTS : The volunteers tolerated the study well. There were no adverse events detected or reported for the study.

M. COMMENTS REGARDING THE BIOEQUIVALENCY STUDY : From Tables 1.1, it could be seen that the mean levels and their coefficients of variation are similar and comparable between test and reference products. Table 1.2 indicates that the mean pharmacokinetic parameter differences met the limits of two one sided test criterion implying equivalence under fasting conditions. The AUC_t is more than 96% of the AUC_{inf} indicating adequate sampling duration. The mean $T_{1/2}$ and Tmax values are comparable between test and reference products.

VI. BIO-STUDY PROTOCOL NO. KETO 9413, POST PRANDIAL STUDY

A. TITLE : Single dose bioequivalence investigation comparing Mylan Ketoprofen capsules (75 mg) with Orudis^R (Wyeth-Ayerst) capsules (75 mg): Food study

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY :

1. Principal Investig

2. Bio-Study :

3. Analytical Investigator : Patrick K. Noonan, Ph.D.

4. Clinical Phase : October 27-November 11, 1994
   Analytical Phase : November 14, 1994-January 4, 1995.

C. STUDY OBJECTIVE : To compare the oral absorption and elimination of two formulations of Ketoprofen capsules following administration of 75 mg dose under fed conditions.

D. STUDY DESIGN : This was a three-way crossover design involving 21 healthy male volunteers. Twenty-one healthy male volunteers were accepted for entry into the clinical phase of the study. All twenty-one subjects completed the three phases of the clinical portions of the study. There was a seven day duration between the three dosing periods (October 27, November 3 and 10, 1994).

E. SUBJECT SELECTION CRITERIA : Similar to the previous study.

F. SUBJECT RESTRICTIONS : Similar to the previous study.

G. STUDY SCHEDULES :

1. **Methods** : Each treatment consisted of the administration of 75 mg ketoprofen (1*75 mg capsule) with 240ml water. Those subjects receiving treatments A and B (fed) received a standardized breakfast approximately 30 minutes prior to dosing. Breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hashed brown potatoes, 6 ounces of orange juice and 8 ounces of whole milk. Subjects receiving treatment C (fasting) fasted for 10 hr prior to dosing. Lunch was served four hours after dosing. Dinner was served 10 hr. after dosing. Liquids were not allowed from 1 hr before until 1 hr after dosing, except for the dosing water and breakfast fluids.

2. **Randomization Schedule** : The following randomization schedule was seen:

Treatments			
Phase I	Phase II	Phase III	Volunteer Number
A	B	C	5, 8, 16, 19
A	C	B	3, 10, 14
B	A	C	2, 12, 15, 20
B	C	A	6, 11, 17
C	A	B	1, 9, 18, 21
C	B	A	4, 7, 13

3. **Blood Sampling** : Serial blood samples were collected from each subject pre-dose (0 hr) and at 0.17, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24hr following dosing. The blood samples were collected in heparinized Vacutainers. Plasma samples were separated and stored at -20^{0}C in the acidified (40% citric acid) vials until analysis.

H. DRUG TREATMENTS :

1. TEST PRODUCT A : Ketoprofen Capsule, 75 mg {1*75 mg} (Mylan Labs) with food, Lot # 2A002H, Assay Potency=97.0%, Batch Size=

2. REFERENCE PRODUCT B : Orudis^R Capsule, 75 mg {1*75 mg} (Wyeth-Ayerst) with food, Lot # 9930192, Assay Potency=99.1%, Expiry date: 01/96

3. REFERENCE PRODUCT C : Ketoprofen Capsule, 75 mg {1*75 mg} (Mylan Labs) fasting, Lot # 2A002H, Assay Potency=97.0%, Batch Size=

I. ASSAY METHODOLOGY : Similar to the previous study

J. PHARMACOKINETICS AND STATISTICS : The pharmacokinetic parameters were calculated similar to the previous study. The statistical evaluation was done using point estimates.

K. RESULTS OF THE POST PRANDIAL BIO-STUDY : The plasma level time data are given in Table 2.1. The mean pharmacokinetic parameters and the corresponding statistics are given in Table 2.2. The mean pharmacokinetic profiles are given in Attachment 2.3. The plasma levels are expressed as microgram/ml, AUC as (microgram/ml)*hr, and Tmax and half-life as hours.

Table 2.1 : Mean Plasma level data, ug/ml (N=21) ± Standard Error

Time (hr)	Mylan (fed), TRT A	Ref. (fed), TRT B	Mylan (fast), TRT C
0.0	0.0 (---)	0.0 (---)	0.0 (---)
0.17	0.01 (0.01)	0.03 (0.03)	0.07 (0.02)
0.33	0.31 (0.15)	0.15 (0.05)	2.30 (0.40)
0.5	0.67 (0.28)	0.50 (0.12)	4.63 (0.76)
0.75	1.19 (0.36)	1.56 (0.33)	4.87 (0.56)
1.0	1.43 (0.32)	2.13 (0.38)	4.50 (0.52)
1.25	1.83 (0.30)	2.37 (0.33)	3.84 (0.32)
1.5	2.08 (0.27)	2.63 (0.30)	3.55 (0.24)
2.0	2.31 (0.18)	2.59 (0.19)	2.53 (0.13)
3.0	2.24 (0.14)	2.07 (0.10)	1.68 (0.16)
4.0	1.83 (0.17)	1.91 (0.20)	0.97 (0.08)
5.0	1.00 (0.09)	1.01 (0.11)	0.67 (0.14)
6.0	0.54 (0.05)	0.54 (0.06)	0.40 (0.09)
7.0	0.32 (0.03)	0.31 (0.04)	0.22 (0.02)
8.0	0.21 (0.03)	0.20 (0.03)	0.14 (0.03)
10.0	0.11 (0.02)	0.11 (0.03)	0.04 (0.02)
12.0	0.04 (0.02)	0.03 (0.02)	0.01 (0.01)
16.0	0.00 (---)	0.00 (---	0.00 (---)
24.0	0.00 (---)	0.00 (---	0.00 (---)

Table 2.2 : Mean Pharmacokinetic Parameters ± Standard Deviation, N=21

PK Parameter	TRT A, Mylan Fed	TRT B, Ref Fed	TRT C, Mylan Fast	Ratio (A/B)
AUC_t	10.20 (2.02)	10.84 (2.14)	12.03 (2.22)	0.94
$LnAUC_t$	2.30 (0.20)	2.37 (0.20)	2.47 (0.18)	0.97
AUC_{inf}	10.86 (2.21)	11.57 (2.62)	12.39 (2.26)	0.94
$LnAUC_{inf}$	2.37 (0.21)	2.43 (0.22)	2.50 (0.18)	0.98
Cmax	3.24 (1.04)	3.56 (1.10)	6.20 (2.67)	0.91
LnCmax	1.13 (0.29)	1.23 (0.30)	1.74 (0.43)	0.92
Tmax	2.35 (1.11)	2.27 (1.21)	1.36 (1.19)	1.04
$T_{1/2}$	2.58 (2.66)	2.98 (3.68)	1.87 (0.59)	0.87

L. ADVERSE EFFECTS : There were no adverse events reported in the study.

M. COMMENTS FOR THE POST PRANDIAL BIO-STUDY : From Table 2.1 , it can be seen that the mean plasma levels and their standard errors are comparable between test and reference products. Table 2.2 indicated that the mean ratio of various pharmacokinetic parameters following the food treatment is more than 0.91 suggesting formulation equivalence after the food challenge. The Tmax and half-life values are also comparable. When compared to the fasting treatment, the food challenge appears to have delayed the drug absorption. The Cmax is also reduced. These observations thus confirm the labelling information. The extent of absorption however has not altered much. AUC_t values are more than 93% of the AUC_{inf} values indicating adequate sampling duration.

VII.DISSOLUTION METHODOLOGY : The following methodology was used for the comparative dissolution of the test and reference capsule formulations.

Apparatus: USP XXIII Apparatus II (paddle)
Speed: 50 rpm
Medium: 0.05M Potassium Phosphate Buffer

Volume: 1000 ml

A. RESULTS OF THE DISSOLUTION TESTING : The dissolution testing data and results are seen in Table D1.

B. COMMENTS ABOUT THE DISSOLUTION TESTING :

1. The dissolutions are conducted as per the FDA dissolution method and specifications for Ketoprofen capsule are described in the FDA dissolution handbook. At present USP does not have a recommended dissolution method or specification for Ketoprofen.

2. Though the ,for 50 mg) and (for 75 mg) mean dissolutions differ considerably, both formulations pass the minute dissolution FDA specification 'Q' comfortably.

VIII.OVERALL COMMENTS :

1. Based on the provided study results, dissolution data and analytical validation, the 75 mg formulations appear to be bioequivalent. Based on the formulation proportionality coupled with comparable dissolution, the 50 mg formulations can be deemed bioequivalent.

2. The firm has modified the formulation from the previous one, by i) Using active ingredient instead of used previously and ii) By altering the inactives qualitatively and quantitatively. The new capsule weight is 300 mg compared to 250 mg for the previous formulation. Since the firm has conducted acceptable bio-studies using this new formulation, in-future, the dissolution profiles of this new formulation would be used as the reference.

IX.RECOMMENDATIONS :

1. The dissolution testing data conducted by Mylan Labs on its Ketoprofen 75 mg and 50 mg capsule formulations, lot #'s 2A002H and 2A001H respectively are acceptable.

2. The bioequivalence study conducted by Mylan labs. on its 75 mg capsule, lot # 2A002H, comparing it to Wyeth Ayerst's Orudis^{R}, 75 mg capsule, Lot # 9930192 has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan labs's ketoprofen 75 mg capsule is bioequivalent to the reference product, Orudis^{R}, 75 mg capsule manufactured by Wyeth-Ayerst.

3. The firm has conducted an acceptable in-vivo bioequivalence study, comparing its 75 mg capsule of the test product with 75 mg capsule of the reference product Orudis^{R} manufactured by Wyeth-Ayerst Labs. The formulation for the 50 mg strength is proportionally similar to the 75 mg strength of the test product

which underwent bioequivalency testing. The waiver of in-vivo bioequivalence study requirements for the 50 mg capsule of the test product is granted. The 50 mg Ketoprofen capsule of the test product is therefore deemed bioequivalent to the 50 mg capsule of Orudis^{R} manufactured by Wyeth-Ayerst.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 ml of pH 7.4, 0.05M Potassium Phosphate Buffer at 37^{0}C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labelled amount of the drug in the dosage form is dissolved in 30 minutes.

5. From the Bioequivalence point of view the firm has met the requirements of in-vivo bioequivalency and in-vitro dissolution testing and the application is acceptable.

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG 1/24/96

Concur: Date: 2/2/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-035(Original, Duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Sathe), Drug File, Division File.

Table D1. In Vitro Dissolution Testing

Drug (Generic Name): Ketoprofen Capsule
Dose Strength: 75 mg and 50 mg
ANDA No.: 74-035
Firm: Mylan Labs
Submission Date: May 23, 1995

I. Conditions for Dissolution Testing:

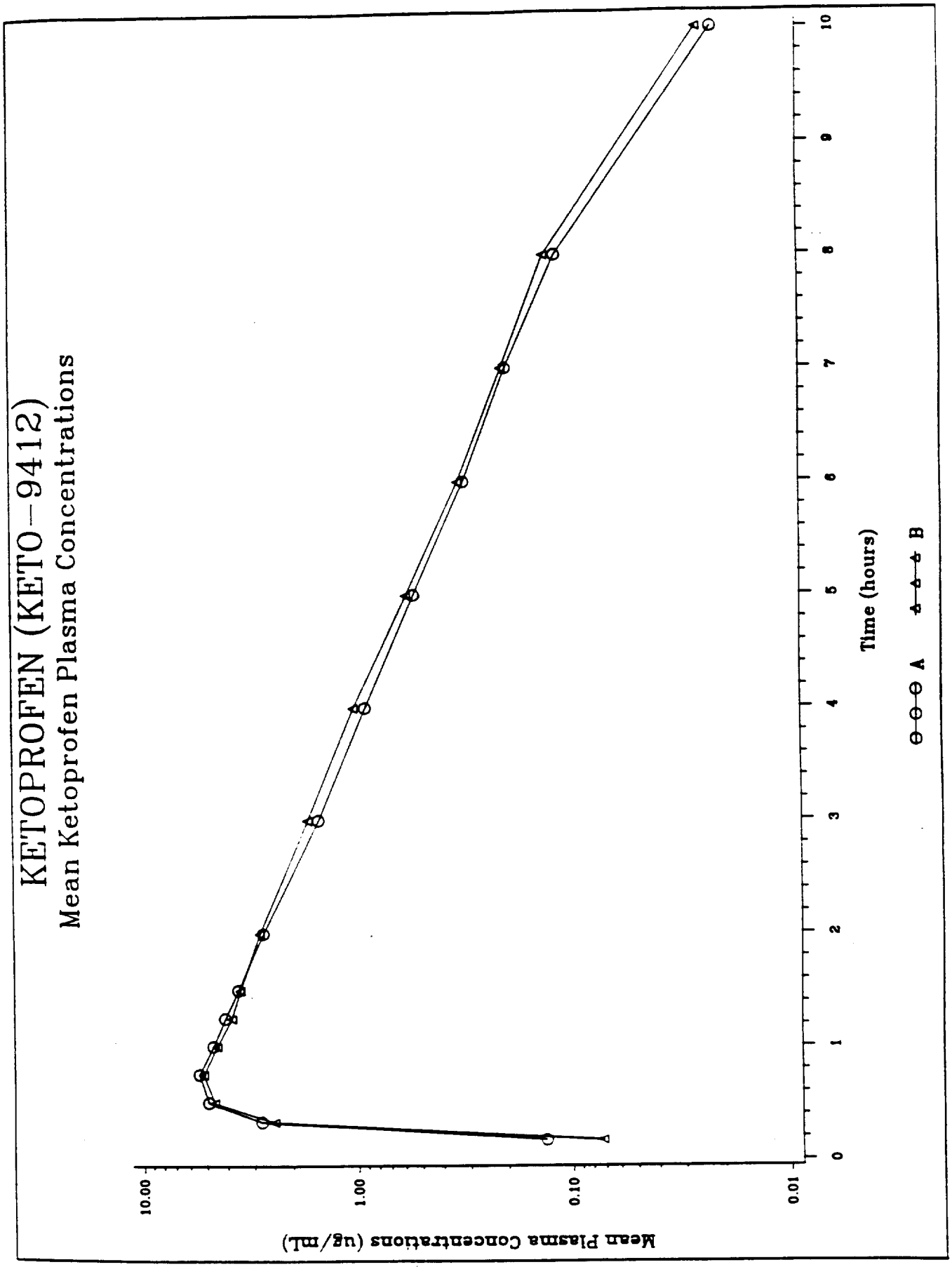
USP XXIII Paddle RPM: 50
No. Units Tested: 12
Medium: pH 7.4, 0.05M Potassium Phosphate Buffer
Volume: 1000ml
Specifications: NLT (Q) in 30 minutes
Reference Drug: Orudis^{R} by Wyeth-Ayerst
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product : Mylan's Ketoprofen Capsule Lot # 2A001H Strength (50 mg)			Reference Product : Wyeth Ayerst's Orudis^{R} Lot # 9930190 Strength (50 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	74.0		6.2	60.2		10.3
20	88.0		3.3	88.1		6.7
30	92.9		2.2	95.9		4.3

Sampling Times (Minutes)	Test Product : Mylan's Ketoprofen Capsule Lot # 2A002H Strength (75 mg)			Reference Product : Wyeth Ayerst's Orudis^{R} Lot # 9930192 Strength (75 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	79.1		10.3	45.4		12.3
20	90.6		4.7	64.1		14.8
30	95.3		3.3	93.6		3.0

Attachment 1.3



Attachment 2-3